NICE National Institute for Health and Care Excellence

NICE guidance

Genedrive MT-RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies: early value assessment

HealthTech guidance
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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces MIB290 and HTE6.

1 Recommendations

1.1 The Genedrive MT-RNR1 ID Kit can be used while further evidence is generated as an option for detecting the genetic variant m.1555A>G to guide antibiotic (aminoglycoside) use and prevent hearing loss in newborns who are being considered for treatment with aminoglycosides.

1.2 Healthcare professionals should tell parents about the possible implications of positive test results for their baby and their family at an appropriate time, and give support and information.

1.3 Positive results should be confirmed by laboratory testing.

1.4 The recommendation is conditional on further evidence being generated on:

- how the test affects time to antibiotics
- how the test result affects antibiotic prescribing decisions
- the technical performance and accuracy of the test.

See the evidence-generation plan for further information on the prioritised evidence gaps and outcomes, ongoing studies, potential real-world data sources, and how remaining evidence gaps can be resolved through the design of real-world evidence studies.

Potential benefits of early access

- **Clinical:** Evidence suggests that the Genedrive MT-RNR1 ID Kit quickly and accurately identifies babies with the MT-RNR1 m.1555A>G variant, who may be at risk of hearing loss if given aminoglycoside antibiotics. This will allow equally effective alternative antibiotics to be used instead.
- **Unmet need:** There is currently no test available in the NHS that gives results quickly enough to inform decisions on acute antibiotic prescribing.
- **Resources:** The long-term savings to the NHS associated with hearing loss and fitting cochlear implants could be substantial.

Managing the risk of early access

- **Time to antibiotics:** Evidence suggests that time to antibiotics is not affected by implementing the test, but the evidence was mostly generated in 1 large specialist neonatal intensive care unit. The test should be implemented in a treatment plan that aims to deliver antibiotics within 1 hour only if it does not cause a delay. Data on time to antibiotics should be collected in a range of centres and settings, including smaller non-specialist centres and outside neonatal intensive care units.
- **Antibiotic resistance:** The alternative antibiotics are associated with an increased risk of antibiotic resistance. The risk is likely to be small because the genetic variant is not common, so very few babies will be treated with the alternative antibiotics. The test should not be used to drive unnecessary use of alternative antibiotics associated with an increased risk of antibiotic resistance. Evidence should be generated on how the test result affects antibiotic prescribing decisions.
- **Accuracy and technical performance:** Evidence suggests the test has high accuracy, but there is uncertainty because the genetic variant is not common, so the study results are based on a small number of positive cases. The test was also updated during the study to reduce the failure rate; real-world data suggests the failure rate with the current version of the test is low. Further evidence should be collected to reduce this uncertainty. Because of the risk of false positive results, positive results should be confirmed by laboratory testing to make sure

that only true positive results are added to people's medical records.

- **Costs:** The economic evidence suggests the test could be cost effective, but the upfront costs of buying the Genedrive system may be high. This guidance will be reviewed within 4 years and the recommendations may change. Take this into account when negotiating payment options and the length of contracts.
- **Equality:** The prevalence of the genetic variant differs between ethnic backgrounds. There are also other variants associated with a risk of hearing loss. Data should be generated in centres with babies from different ethnicities to promote equality. The test should also be implemented in a wide range of geographical regions to include patients from various socioeconomic groups to ensure equal access.

2 The technology

Clinical need and practice

2.1 Neonatal bacterial infection is a significant cause of death and illness in newborn babies. NICE's guideline on neonatal infection recommends treating suspected early-onset infection in babies with benzylpenicillin with gentamicin and that this should be given as soon as possible and always within 1 hour of the decision to treat.

2.2 Babies with a genetic variant in the mitochondrial MT-RNR1 gene (m.1555A>G) are at an increased risk of profound bilateral deafness caused by damage to the ear (ototoxicity) if they have treatment with the aminoglycoside family of antibiotics, which includes gentamicin.

2.3 Currently available laboratory testing for m.1555A>G cannot provide results quickly enough to inform antibiotic prescribing in babies with a suspected infection that needs to be treated within 1 hour.

The intervention

2.4 The Genedrive MT-RNR1 ID Kit (Genedrive plc) is a qualitative in vitro molecular diagnostic test for detecting the MT-RNR1 m.1555A>G variant. It is intended to be used by healthcare professionals in a near patient setting using a buccal (cheek) swab sample. The company says that the kit provides a result within about 26 minutes. This could help ensure that babies who have the m.1555A>G variant have alternative antibiotics and avoid irreversible, lifelong hearing loss caused by ototoxicity. The Genedrive MT-RNR1 ID kit costs £100 (excluding VAT). The cost per test used in the economic model (incorporating additional cost components such as purchase of the Genedrive machine, printing costs, control tests, warranty and staff costs) was £130.08.

The comparator

2.5 The comparator is to not test to determine the baby's MT-RNR1 m.1555 variant status before treatment with aminoglycosides.

3 Committee discussion

The diagnostics advisory committee considered evidence on the Genedrive MT-RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies from several sources, including an early value assessment report and an overview of that report. Full details are in the project documents for this guidance.

Patient and carer considerations

3.1 A patient expert explained the impact that aminoglycoside-induced hearing loss has on children and their families. Parents and families are already under considerable stress when a baby is admitted to a neonatal unit because of suspected infection. When hearing loss does occur, it is a shock and can cause a mix of emotions, including confusion, anger, sadness, disbelief and guilt. The patient expert noted that these emotions could be made worse if they knew a test existed that could have prevented this. It can be difficult for parents to explain to other family members and friends. Parents have several concerns and unanswered questions around how severe the hearing loss may be, how it will affect their child's ability to communicate and develop language skills, and what support or treatment they may need. They highlighted that the severity of hearing loss and its effects can vary between children. Children with hearing loss have reduced access to spoken language, which affects their ability to communicate, as well as their social and emotional development. It can also affect their education and employment opportunities in the future. The committee concluded that aminoglycoside-induced hearing loss has a major impact on the quality of life of children and their families.

Equality considerations

3.2 The committee discussed how the prevalence of the m.1555A>G variant differs between ethnic backgrounds. It said that further evidence should be generated in centres with different patient demographics, for example with different proportions of people from diverse ethnicities. The committee also considered equity of access and noted that it would be

necessary to ensure that the test was implemented in a wide range of geographical regions, to include patients from various socioeconomic groups. It concluded that these implementation considerations would be essential to avoid inequalities.

Clinical effectiveness

Time to antibiotic treatment

3.3 Evidence on time to antibiotic treatment from the PALOH study (McDermott et al. 2022) showed no statistically significant difference between standard care and when using the Genedrive test. The PALOH study was a prospective observational implementation trial based in 2 large specialist neonatal intensive care units. But most of the data (94% of babies recruited) was from 1 of these units. A clinical expert said that it was uncertain if the result from the PALOH study was generalisable to other settings, such as smaller non-specialist centres or outside of a neonatal intensive care unit (on a labour ward, for example). There may be differences in how wards are set up and the experience of staff in implementing new technologies, or there may be more demands on staff time. The committee noted that one of the centres in the PALOH study now routinely tests all babies on admission to the neonatal intensive care unit. But it said that individual centres should decide which babies to test depending on local knowledge of what proportion of babies go on to receive aminoglycosides. The clinical expert explained that time to antibiotic treatment is very important for the efficacy of the antibiotics, but it is often a challenge in standard care to ensure that antibiotics are administered within 1 hour. However, another clinical expert said that, of those babies that were prescribed antibiotics based on clinical suspicion of infection (10% to 12% of all babies), only a small proportion would benefit from this treatment being delivered within the hour (around 1%). This is because in a lot of cases, with hindsight, the antibiotics were not needed because there was no infection. However, they are given because the consequences of missing the small proportion who benefit would be severe. The committee agreed that further evidence in alternative settings was needed, but it also agreed the risk was low if the test was introduced while further evidence was generated on time to

antibiotics. It concluded that the benefits of using the test and preventing aminoglycoside-induced hearing loss in susceptible babies outweighed this risk.

Antibiotic prescribing

3.4 A clinical expert explained that the reason gentamicin is the first-choice antibiotic is because it is active against a wide range of bacteria (Gram-negative bacteria and *Staphylococcus aureus*) and has a low risk of increasing antibiotic resistance. They said that other antibiotics such as cefotaxime (a cephalosporin) are equally effective and have a better safety profile but are not the first choice because using them can lead to an increase in antibiotic resistance. In the PALOH study, babies that needed antibiotics and were found to have the m.1555A>G variant were treated with cefotaxime. A clinical expert said that if the test was implemented, failed tests and false positive results could lead to more widespread use of alternative antibiotics that may promote antibiotic resistance. The committee said that this would not be a concern if the failure rate and false positive rates remained low, but noted that there was some uncertainty in this data (see the sections on test failure rate and diagnostic accuracy). The committee said that this should be monitored closely and alternative antibiotics should be used when the test is positive. When the test fails and there is no time for a second test to be done, NICE's guideline on neonatal infection should be followed alongside local prescribing protocols. The committee concluded that, although alternative antibiotics are associated with increased antibiotic resistance, a relatively small number of babies would be treated with them if the real-world false positive rate was low. Therefore, if the Genedrive test was implemented, it should not lead to increased antibiotic resistance in neonatal units. The committee also concluded that the alternative antibiotics were likely to be equally effective, so there were no concerns around treating babies with an alternative if they have the m.1555A>G variant.

Test failure rate

3.5 The PALOH study reported an initial failure rate of 17.1% for the Genedrive test. This was reduced to 5.7% after modifications to the test buffer. The

committee said that it had some concerns about the test being modified during the study and whether the reported improvement in the failure rate would be replicated in real-world use. A clinical expert said that if the test failed, clinicians may decide to use an alternative antibiotic. In many cases, this would be unnecessary and could promote the spread of antibiotic resistance. They said that failed tests could also lead to delays to antibiotic treatment. However, the company said the PALOH study was an implementation study and the results were used to update the test. The updated test is currently in use at Saint Mary's Hospital in Manchester and is the commercially available Genedrive MT-RNR1 ID Kit. Comments from the Manchester Centre for Genomic Medicine said that the current failure rate in real-world use since PALOH is 1.81% (95% confidence interval [CI] 0.6% to 5.18%). The committee noted that this was promising but was based on data from a large specialist neonatal intensive care unit and may not generalise to all settings where the test may be used. It said that further data should be collected on the real-world failure rate of the Genedrive test in different settings. The committee concluded that, although there was some uncertainty around the failure rate of the test, this did not present a risk to the babies being tested and the test could reduce the risk of aminoglycoside-induced hearing loss. It also concluded that data on the failure rate could be collected as part of real-world evidence generation.

Diagnostic accuracy of the test

3.6 No false negative results were reported in the PALOH study, but only 3 babies were identified with the m.1555A>G variant (true positives). So, although the reported sensitivity estimate was high at 100%, there was still considerable uncertainty about the value (95% CI 29.2% to 100%). The committee noted that it would be difficult to reduce this uncertainty without a very large study because of the low prevalence of the m.1555A>G variant in the population (around 0.19%). A clinical expert explained that hearing loss can occur soon after exposure to aminoglycosides, but in some babies it might be after they have passed the newborn hearing test. For babies that develop hearing loss later, it can be more difficult to link it to their exposure to aminoglycosides, so it may be difficult to follow up and identify babies that had a false negative result in a real-world setting. But the clinical experts said that they were

not concerned about false negative results because at the moment there is no testing at all. So even with a risk of false negatives, any testing improves the chance of babies with the m.1555A>G variant being identified and reduces the risk of them receiving aminoglycosides. The PALOH study also reported 5 false positive results. The authors said that this was corrected with an updated test cartridge design. The committee said that false positive results did not pose any particular risk to babies because they would be treated with an alternative, equally effective, antibiotic. However, it reiterated its concerns about the test being updated during the study and noted that it was uncertain whether changes made to reduce the false positive rate could affect the sensitivity. The committee concluded that there was some uncertainty in the estimated sensitivity of the Genedrive test. It said that post-market surveillance could be used to follow up babies that test negative on the Genedrive test but later go on to develop hearing loss. Retrospective laboratory testing of these babies, in addition to routine confirmatory testing of babies with a positive result, should be done to help improve the precision of the sensitivity estimate and confirm the real-world false positive rate.

Risk of aminoglycoside-induced hearing loss

3.7 The external assessment group (EAG) said that there was clear evidence that the m.1555A>G variant is a risk factor for aminoglycoside-induced hearing loss. However, the evidence is from case-control studies that may overestimate this risk, so the precise level of risk is uncertain. The committee said that it would be difficult to use an alternative study design because of ethical concerns, so it would likely always be uncertain. Other variants in the MT-RNR1 gene are also associated with a risk of aminoglycoside-induced hearing loss. Therefore, it considered that babies who test negative for the m.1555A>G variant but still go on to develop hearing loss should be followed up with laboratory testing to determine if they have had a false negative result. Depending on developments in laboratory testing, in the future it may also be possible to determine if they have a different MT-RNR1 variant. A clinical expert said that mitochondrial whole genome sequencing could also be considered to look for different variants if clinically indicated. The committee concluded that, although there was some uncertainty around

the risk and severity of hearing loss, further evidence generation would be unlikely to address this.

Cost effectiveness

Upfront costs

3.8 Implementing the Genedrive test with real-world data collection would incur upfront costs that would be lost to the NHS (that is, sunken costs) if it is later shown not to be value for money. The committee considered that these upfront costs included the Genedrive MT-RNR1 ID system (£4,995) and Bluetooth printer (£400). A clinical expert said that centres may need more than 1 Genedrive system to successfully implement the test, and the company noted that Saint Mary's Hospital in Manchester has 2 systems in use. The EAG noted that this would not substantially affect the cost per test because of the high volume of testing and expected lifespan of the equipment. However, the committee concluded that the upfront costs of implementing the Genedrive test should be carefully considered by commissioners. It noted that purchase options not involving large capital investment costs should be explored for any conditional recommendation and real-world data collection.

Model assumptions

3.9 The EAG's early economic model made a number of key assumptions. It assumed no effect on time to antibiotic treatment when using the Genedrive test, so the consequences of any delay were not included in the economic analysis (see the section on time to antibiotic treatment). The EAG explained that it made a pragmatic decision to assume no effect on the time to antibiotics (as reported in the PALOH study). It also said that the data on time to antibiotics and outcomes was uncertain. The committee said that any future model for a full diagnostics evaluation and guidance should include time to antibiotic treatment and explore how any delays to antibiotics affect clinical outcomes. The model used the high diagnostic accuracy estimates reported in the PALOH study, which the committee recalled had some uncertainty around them (see the section on diagnostic accuracy). The committee noted that the early model also

assumed that all babies with the m.1555A>G variant treated with aminoglycosides had severe or profound hearing loss. It said that the true risk and severity of deafness was difficult to estimate and would likely always be uncertain because it would be difficult to study (see the section on risk of aminoglycoside-induced hearing loss). The committee concluded that, overall, the model assumptions were reasonable, but that any future model to be used for full guidance recommendations should include time to antibiotic treatment and its associated outcomes.

Cost effectiveness

3.10 The committee noted the high cost of identifying 1 baby with the m.1555A>G variant because it is relatively uncommon in the population. But the EAG's early economic model showed that the Genedrive test has the potential to be cost effective because over the lifetime of the baby, it is cheaper and more effective than standard care. The committee said that this was based on a number of assumptions, as previously mentioned, but it understood that hearing loss is associated with substantial healthcare costs and can have a major impact on quality of life. It also noted that the sensitivity analysis showed that changing these assumptions was unlikely to change the model conclusions. A patient expert highlighted the wider societal costs and educational impact of hearing loss. The committee noted that these costs were not captured in the model. It said that, although these are important considerations, they are outside of the NICE reference case. The committee also considered the potential additional benefits of avoiding aminoglycoside exposure in the future but noted that these were not included in the cost-effectiveness analysis. The committee concluded that, based on the early economic model results, the Genedrive test had the potential to be cost effective over a lifetime.

Evidence generation considerations

Patient demographics and ethnicity

3.11 The prevalence of the m.1555A>G variant varies between different ethnicities, so the committee considered that any further evidence

generation should ensure that the Genedrive test is implemented in centres with babies from different patient demographics, for example with different proportions of patients from diverse ethnicities (see the section on equality considerations).

Data should be collected in smaller, non-specialist centres

3.12 The committee said that further evidence generation should include smaller, non-specialist centres and other settings outside of neonatal intensive care units where the test may be used. This is to ensure that the evidence generated can help assess if the time to antibiotic treatment, test failure rate and diagnostic accuracy estimates reported in the PALOH study are generalisable to other settings. This will also reveal what effect test implementation has on antibiotic prescribing decisions in different centres and settings.

Test implementation and equity of access

3.13 The committee said that if the test was implemented for further evidence generation, this should be done in a wide range of geographical regions to ensure equal access to patients from different socioeconomic groups.

4 Evidence generation recommendations

4.1 Further evidence generation is recommended on:

- how the test affects time to antibiotics in smaller, non-specialist centres and outside of neonatal intensive care units
- how the test result affects antibiotic prescribing decisions
- the failure rate of the test
- the diagnostic accuracy of the test.

See the evidence-generation plan for further information on the prioritised evidence gaps and outcomes, ongoing studies, potential real-world data sources, and how remaining evidence gaps can be resolved through the design of real-world evidence studies.

5 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE, and specialist committee members.

Committee members are asked to declare any interests in the test to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each diagnostics evaluation is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Sophie Harrison and Simon Webster
Topic leads

Judith Shore
Technical adviser

Harriet Wilson
Project manager

Update information

August 2023: NICE has developed tools and resources, in association with relevant stakeholders, to help organisations put this guidance into practice, including an evidence-generation plan. The evidence-generation plan discusses the prioritised evidence gaps and outcomes, ongoing studies, potential real-world data sources, and how remaining evidence gaps can be resolved through the design of real-world evidence studies.

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